Remarks/Arguments

Claims 1-3, 8-14 and 16 are pending in this application and stand rejected on various grounds.

(1) Claims 1-3, 8-14 and 16 have been rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over US Patent No. 5,525,625 (the '625 patent) in view of WO 98/02540 and WO 01/15730.

The '625 patent was cited as allegedly teaching a method of treating proliferative disorders, such as psoriasis and cancer, by administering a MAP kinase inhibitor such as 2-(2-amino-3-methoxyphenyl)-4-oxo-4H[1]benzopyran. According to the rejection, the invention claimed in the present application "differs from the teachings of the reference only in that the method of therapeutic treatment [of] psoriasis is an antibody that binds to ErbB2 and blocks ErbB2 signaling through the MAP kinase pathway." (Office Action, page 2, past paragraph)

WO 98/02540 was cited as allegedly teaching that ErbB2 plays a role in psoriasis and a method of treating psoriasis by administering to a mammal an agent that blocks the ErbB2 ligand from binding to its receptor, ErbB2. According to the rejection, this document "teaches blocking ErbB2 using ErbB antagonist such as ErbB2 and ErbB3 or ErbB2 and ErbB4 fused to Fc prevents the ErbB ligand from binding and activation of the ErbB receptor." (Office Action, page 3, first paragraph)

WO 01/15730 was cited as allegedly teaching a method of treating a benign hyperproliferative epithelial, inflammatory angiogenic immunological disorder by administering an effective amount of an antibody which binds ErbB2.

According to the rejection, "it would have been obvious to one of ordinary skill in the art at the time the invention was made to treat psoriasis by substituting the MAP kinase inhibitor 2-(2-amino-3-methoxyphenyl)-4-oxo-4H[1]benzopyran of the '625 patent or the ErbB2-IgG immunoadhesin that blocks ErbB2ligand from binding to ErbB2 as taught by the WO 98/02540 publication for the antibody or binding fragment thereof that binds to ErbB2 and

thereby preventing the binding of ErbB2 ligand to its receptor as taught by the WO 01/15730 publication." (Office Action, passage bridging pages 3 and 4)

Motivation was found in the '625 patent's alleged teaching that a MAP kinase inhibitor is useful for treating psoriasis. In particular, the Examiner states: "One having ordinary skill in the art would have been motivated to do this [i.e. to combine the cited references] because the '625 patent teaches MAP tyrosine kinase inhibitor is useful for treating psoriasis, see claims of the '625 patent." (Office Action, page 4, first full paragraph)

In addressing Applicants' arguments concerning WO 98/02540 submitted in response to the previous Office Action, the Examiner asserts that the teaching of US Patent No. 5,525,625 of a tyrosine kinase inhibitor blocking the MAP kinase pathway to treat psoriasis creates a reasonable expectation of success that psoriasis can be treated with the antibodies of the present invention. The Examiner further notes that the MCF7 cells used in the experiments disclosed in the present application "are not even the right cell types (model) to be responsible for the chronic psoriasis," and "there is no evidence in the specification as filed that any patient with psoriasis has been treated with anti-ErbB antibody such as rhuMab 2C4 or humanized 6F3 antibody." (Office Action, passage bridging pages 4 and 5)

Applicants respectfully traverse the rejection.

It is unclear how the latter comments, concerning the experimental data presented in the specification, are pertinent to the issue of obviousness, and are therefore not addressed here.

U.S. Patent No. 5,525,625 creates no motivation to treat psoriasis as claimed in the present application.

The '625 patent purports to disclose a highly specific small molecule inhibitor of the MEK kinase activity, which inhibits the phosphorylation of MAP kinase by MEK, thus preventing the activation of MAP kinase in cells in which the Ras cascade has been activated.

According to the '625 patent, the highly selective MEK inhibitory activity of the disclosed compound is unexpected, as several close analogues of the claimed compound were known to be poor inhibitors of MEK, and there were no prior known selective MEK inhibitors known in the art. (See, e.g. the Background of the Invention section of the '625 patent).

The assertion that U.S. Patent No. 5,525,625 creates a motivation to treat psoriasis with anti-ErbB2 antibodies blocking ErbB2 signaling through the MAP kinase pathway, as claimed in the present application, is inherently based on the assumption that the anti-ErbB2 antibodies of the present invention can be substituted for a small molecule MAP kinase inhibitor, such as 2-(2-amino-3-methoxyphenyl)-4-oxo-4H[1]benzopyran of the '625 patent. The Examiner's attention is respectfully directed to the Federal Circuit's decision in Takeda Chem. Indus., Ltd. vs. Alphapharm Pty., Ltd. , 492 F.3d 1350 (Fed. Cir. 2007), reaffirming the long established requirement that in order to establish obviousness for chemical compounds, it is necessary to establish a motivation to modify a chemical compound in a certain way in order to arrive at the allegedly obvious compound. In the present case, the chemical compound disclosed in the '625 patent is a small molecule MAP kinase inhibitor. The Examiner has shown no motivation to modify this small molecule inhibitor in a manner that would result in the making of an antibody, in particular an anti-ErbB2 antibody. The small molecule inhibitor of '625 and the anti-ErbB2 antibodies of the present invention are chemically completely unrelated, therefore, the '625 patent does not create any motivation for making and using the anti-ErbB2 antibodies of the present invention to treat psoriasis. This is particularly true in view of the '625 patent's teaching that even compounds closely related to 2-(2-amino-3-methoxyphenyl)-4-oxo-4H[1]benzopyran did not have the requisite activity.

The cited combination of references does not create a reasonable expectation of success

As explained in response to a prior similar rejection, WO 98/02540, when read without the benefic of the teaching of the present application, does not have a clear an unambiguous teaching for the treatment of psoriasis by administration of an agent that blocks the ErbB2 ligand from binding to its receptor. Psoriasis is listed as one of a long laundry list of various

unrelated malignant, neuronal, inflammatory, immunologic, etc. disorders. In order to arrive at the invention claimed in the present application, the skilled artisan would be required to (1) assume that the anti-ErbB2 antibodies of the present invention can somehow be substituted for the small molecule tyrosine kinase inhibitor of the '625 patent, i.e. that the two are chemically equivalent; (2) select the once mentioned psoriasis from among the numerous unrelated diseases and conditions targeted by the heteromultimer adhesins of WO 98/02540, and (3) assume that the anti-ErbB2 antibodies of the other secondary reference, WO 01/15730, will behave the same way as the ErbB heteromultimer adhesins of WO 98/02540. It is clear that one of ordinary skill in the art would not make all these assumptions, especially in view of the unpredictability in the art, also acknowledged by the inventors of the '625 patent, who point out that even structurally closely related small molecule compounds have significantly different properties.

Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

(2) Claims 1-3, 8-14 and 16 were rejected under 35 U.S.C. 1039a) as allegedly being unpatentable over U.S. Patent No. 5,525,625 in view of U.S. Patent No. 5,650,415 and WO 01/15730.

The '625 patent and WO 01/15730 were cited as in the previous rejection. The '415 patent was cited for its alleged teaching that members of the HER family are included among the tyrosine kinases, and that many of these kinases are involved in cellular signaling pathways, leading to pathogenic conditions such as cancer, psoriasis, and hyperimmune response. According to the rejection, "it would have been obvious to one of ordinary skill in the art at the time the invention was made to treat psoriasis by blocking ErbB2 signaling through the MAP kinase pathway by substituting the MAP kinase inhibitor 2-(2amino-3-methoxyphenyl)-4-oxo-4H[1]benzopyran of the '625 patent or the various tyrosine kinase inhibitor [sic] such the compounds as shown in the Summary of the Invention that blocks ErbB2 signaling for treating psoriasis of the '415 patent for the antibody or binding fragment thereof which binds to ErbB2 that is useful for treating benign hyperproliferative epithelial,

inflammatory angiogenic immunological disorders [sic] as taught by the W0 01/15730 publication." (Office Action, page 6) The Examiner adds, without any further explanation: "From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention."

Applicants disagree and respectfully traverse the rejection.

The '625 patent and WO 01/15730 have been discussed above. It has been shown that the '625 patent does not provide motivation for making the purported combination, and that the combination of the '625 patent and WO 01/15730 does not create a reasonable expectation of success for the methods claimed in the present application. The '415 patent does not change this outcome.

Just as the '625 patent, the '415 patent discloses yet another group of small molecules, certain quinoline derivatives, as tyrosine kinase inhibitors. The quinoline compounds are purported to be useful in the treatment of HER2 cell proliferation disorders, EGFR disorders, IGF disorders, KDR/FLK-1 disorders, c-MET related disorders, and PDGFR driven disorders. Psoriasis, as a potential target disease is not listed in connection with HER2, rather as an example of unwanted cell proliferation and/or differentiation that can result from inappropriate EGFR activity. Accordingly, this rejection is even less supported than the previous one. Not only is there no structural equivalence between the quinoline derivatives of the '625 patent and the anti-ErbB2 antibodies of the present invention, the reference to psoriasis in the '625 patent is in the context of EGFR-mediated diseases, and not ErbB2-associated diseases or conditions. Indeed, this rejection is a blatant example of hindsight reasoning, using the disclosure of the present application to create a rejection based on a combination of out of context disclosures from unrelated references, which are only connected by the disclosure of the present application.

Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

In conclusion, all claims pending in this application are believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account 07-1700 (Attorney Docket No. 39766-0205 (123851-181836).

Respectfully submitted,

Date: March 31, 2008

Ginger R. Dreger, Esq.
Reg. No. 33,055

GOODWIN PROCTER LLP
Customer No. 77845
181 Lytton Avenue
Palo Alto, CA 94301
Tel: (650) 752-3100
Fax: (650) 853-1038